Supplemental Amendment/Response for application 10/037, 718 Applicants MCGINNIS ET AL. 14 November 20, 2005; 26 total pages submitted by fax to 571-273-8300

Remarks

Regarding amendments in the Claims and Abstract:

This Supplemental Amendment/Response is essentially self-contained, and there is no need for the Examiner to refer back to the previously filed Amendment/Response of September 2005. Applicants respectfully request that the Examiner examine the new, amended claim listing and associated Remarks herein rather than the claim listing and Remarks in the previously filed Amendment/Response of September 2005. There are differences between some previously filed claims and associated Remarks in the Amendment/Response of September 2005 and those in the present Supplemental Amendment. The Examiner is, however, requested to obtain copies of published paper pages that are referred to herein from the previously filed September 2005 Amendment/Response. Pages from published papers that were included with the September 2005 Amendment/Response are generally not included again with this Supplemental Amendment/Response. **A copy of the Tenth Edition of Merriam-Webster's Collegiate Dictionary giving the definition of "thousands" was inadvertently omitted from the September 2005 Amendment and a few other copies of published paper pages referred to herein will be faxed to the USPTO under a separate cover.**

Claims 6-9 and 15-19 were allowed in the Final Office Action mailed May 13, 2005. Claims 10-14 and 20-24 were rejected in that Final Office Action. In response to the rejection, applicants have canceled claims 10, 12, 13, 20, 22 and 23; and claims 14, 21 and 24 have been amended. Clarification regarding claims 14 and 24 is also respectfully submitted.

Applicants have also amended allowed claims 6 and 16 with a slight change in terminology to make the claims more closely conform to the terminology in the Specification ([0046], [0050]) and newly amended Abstract above. These amendments do not, however, change the scope of either claim. Applicants have also filed new claims 26 -51. New claim 39 is, however, essentially the same (same scope) as former independent claim 3, filed 9/03/2003, which was subsequently allowed, but was canceled to avoid a double patenting rejection in the parent application 09/947, 768, now abandoned.

As is well known, support for claims need not be verbatim ("ipsis verbis" or "in haec verba"), but only described in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention (see, e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116).

Regarding claims 10 and 20 (and their dependent claims) The Examiner has rejected these claims. In response applicants have canceled or amended each of these claims to depend from other previously allowed claims.

Regarding amended claim 11 The limitation *"not human being"* is described. The application describes species generally [0057] ("plants and animals"), [0058], [0151], [0260]. And human species are described particularly [0075], [0181], [0191]. Species that are *"not human"* are thus described, a person of ordinary skill would immediately see this. Further, in In re Johnson the applicant taught an invention genus and invention species within the invention genus; and the Court allowed the applicant to claim *"that genus minus two of those species"* (194 USPQ at 196).

Regarding claims 14 and 24 The Examiner has rejected these claims as indefinite under 35 U.S.C. 112, second paragraph because of the language "thousands of bi-allelic covering markers". Applicants respectfully offer the following clarification. The concept of "thousands of bi-allelic [covering] markers" (in connection with the physical implementation the new, two-dimensional linkage study techniques of this application) using silicon chips or glass slides containing oligonucleotides is described in [0249], [0322], [0323], and [0324]. Included in this description is the paper cited in endnote 8, that is incorporated by reference into the application (Accessing Genetic Information with High-Density DNA Arrays, Mark Chee, et al. Science, vol 274, Oct. 25, 1996, pp. 610 – 614). Other similar papers such as Large Scale Identification, Mapping, and Genotyping of Single-Nucleotide Polymorphisms in the Human Genome, Wang, et. al., Science, May 15, 1998, vol 280, pp. 1077-1081 are referred to in endnote 9.

Applicants respectfully submit that given this description and the knowledge of one of ordinary skill, the limitation "thousands of bi-allelic covering markers" is definite. "Thousands" is the plural of "thousand" meaning literally 2000 or more. Thousands is also a very large number. (See copy of page 1228 of the Tenth Edition of Merriam-Webster's Collegiate Dictionary giving the definition of "thousands" as plural of "thousand".) The abstract of the Chee paper (endnote 8) describes "DNA arrays containing up to 135, 000 probes" and page 610 of this paper (bottom left hand column) describes an "array of a large number of oligonucleotide probes". And the next to last paragraph of the Wang paper (endnote 9) on page 1081 describes a "2000-SNP genotyping chip".

The disadvantages of the conventional, generally slower, nucleic acid sequencing technologies (compared to high-density DNA arrays that use large numbers of oligonucleotide probes) is described in the first column, page 610 of the Chee paper. Both the Chee and Wang papers describe querying the entire human genome (estimated in Chee at 100, 000 genes) using a high-density array (p. 613 Chee and last two paragraphs p. 1081 Wang). No definite upper limit to the number of probes (and by implication number of markers) for the technology is given. It is believed that *"For example, the entire set of ~ 10^{12} 20-nucleotide oligomer probes, or any desired subset, can be synthesized...The number of probes that can be synthesized is limited only by the physical size of the array and the achievable lithographic resolution."* (first paragraph, right hand column p. 610 Chee).

The expressions "thousands of genes", "thousands of oligonucleotides", "thousands of bi-allelic markers" or similar expressions were used in the art at the time of filing of the application and are still being used. These expressions are often used in connection with high-density DNA arrays and specific example numbers (that are in the thousands). The applicants will cite several examples of this usage in the art below.

Given the extensive usage of these expressions and knowledge in the art, applicants respectfully submit the limitation "thousands of bi-allelic covering markers" is definite. In In re Corr (146 USPQ 69), the Court found that the phrase "high styrene resin" was definite and rejected the argument the phrase represented "undue breadth or overclaiming". The Court noted that the specification stated that the "high styrene resin" was a resin such as PLIOLITE S-6B. And the Court stated: *"Appellant's specification taken with the prior art clearly indicates that the styrene resin component of his composition is conventional and many equivalents are known in the art"* (146 USPQ at 71). Applicants respectfully submit that in the present application (as in In re Corr) examples of "thousands" have been given (i.e. 135, 000 probes, and 100, 000 genes in the Chee paper). And numerous equivalents of these examples of "thousands" were known in the art at the time of filing. Applicants will cite evidence that there were such numerous equivalents of "thousands" known in the art in the following two paragraphs.

Supplemental Amendment/Response for application 10/037, 718 Applicants MCGINNIS ET AL.. 17 November 20, 2005; 26 total pages submitted by fax to 571-273-8300

Applicants respectfully direct the Examiner's attention to last paragraph on p. 772 the Fodor paper (Science, 1991, vol. 251, pp. 767-773). This paragraph describes a high-density array with 65, 536 oligonucleotides. The Fodor paper is cited as a reference in the Chee paper (note 5, p. 613). The Cann paper (C R Acad Sci III June 1998; 321(6):443-6) uses the phrase *"thousands of DNA polymorphisms (genetic markers)"* and *"thousands of more stable single nucleotide polymorphisms that detect variation on average once every ~ 1000 base pairs"* (see Abstract p. 443 and p. 445 left column bottom paragraph). The DeRisi paper (Science vol 278 October 1997 pp. 680-686) uses the phrase *"DNA microarrays, consisting of thousands of individual gene sequences printed in a high-density array on a glass slide"* (p. 680 2nd paragraph left most column). The DeRisi paper also describes the amplification of 6000 genes and microarrays with 6400 elements in each array (see p. 685 last paragraph). The Lashkari paper (Proc Natl Acad Sci USA vol 94, pp. 13057-13062 Nov. 1997) describes high density DNA arrays containing 2,479 yeast ORFs and 6, 100 ORFs (see Abstract p.13057 and next to last paragraph p. 13062). The Johnston paper (Current Biology Feb 26, 1998, 8(5) pp. R171-R174) uses the phrases "thousands of genes" and "thousands of DNA fragments" in connection with high-density DNA arrays. And Johnston also describes *"current oligonucleotide chips display all 6000 yeast genes on four 1.28 x 1.28 cm chips.. or 1.8 x 1.8 cm glass slide"* (see Abstract and second paragraph p. R171).

A Nature Genetics Supplement vol 21 January 1999 has a large number of papers on DNA microarrays. For example, the Brown paper describes *"arrays of thousands of discrete DNA sequences (for example, all 6200 known and predicted genes of S. cerevisiae"* (see p. 33 last paragraph). And the Lipshutz paper describes hundreds of thousands of oligonucleotides in an array and gives a specific number example of approximately 300,000 (see Abstract and second paragraph p. 20).

Copies of cited pages in the above papers (rather than all the pages) were included for the Examiner's convenience in the previously filed Amendment/Response of 9/13/05. These are: Chee pp. 610 and 613, Wang pp. 1077 and 1081, Fodor pp. 767 and 772, Cann pp. 443 and 445, DeRisi pp. 680 and 685, Lashkari pp. 13057 and 13062, Johnston p. R171, Brown p. 33 and Lipshutz p. 20.

As stated above, the phrase "thousands of bi-allelic markers" is included under Physical Implementation [0322] of the new, two-dimensional linkage study techniques of this application. Thousands of bi-allelic markers are thus described as a tool or implement for use by two-dimensional linkage study techniques. Indeed at the time the application was filed, the whole field of association studies is looking to use thousands of bi-allelic markers. See for example Risch, N. and Merikangas, K.: The Future of Genetic Studies of Complex Human Diseases. Science, 13 September 1996, vol. 273, pp. 1516-1517 cited in [0027] of the application. This Risch paper (see p. 1517 mid left most column) describes using technological advances to do association testing of five diallelic (or bi-allelic) polymorphisms within each of 100, 000 genes (a total of 500, 000 polymorphisms tested in the association study). And the inventor's paper is a generalization of the Risch and Merikangas analysis [0029]. A copy of the Risch paper will be faxed under a separate cover, was also included with the Amend/Resp of 9/05 and in the IDS.

Another example of the expectation (at the time of filing) in the field of using large numbers of markers (e.g., thousands) from high-density marker maps is the Kruglyak paper. The Kruglyak paper (*The use of a genetic map of bi-allelic markers in linkage studies*, published 9/97, see footnote 4, p.3 of the present application) is quoted in the application (see mid [0026]) as predicting a density of at least 1,000 SNPs (bi-allelic markers) per cM. Since a human chromosome is about 150 cM in length, a density of at least 1,000 bi-allelic markers per cM is about at least 150, 000 bi-allelic markers per chromosome (or at least 3 million bi-allelic markers in the genome). Page 21 (right column) of the Kruglyak paper essentially predicts that this large number (and density) of markers could be practically genotyped using more automated genotyping techniques (p. 24 Kruglyak) that are also described in the present application under Oligonucleotide Technology [0249] in endnote 11 (application p. 25) in references (1) Chee, (2) Saiki, (3) Wu, and (4) Nickerson. (A copy of the Kruglyak paper will be faxed under a separate cover and was also included with the IDS for parent application 09/623,068 (now abandoned)).

Thus the use of thousands of bi-allelic covering markers as recited in claims 14 and 24 is supported and is definite. Even if the process of claim 14 used, for example, 2 million covering markers, it would necessarily use thousands of covering markers and be included in the scope of the claim. And even if there were for example, 2 million covering markers in the group of two or more bi-allelic covering markers as recited in claim 24, there would necessarily be thousands of covering markers in the group. And such an embodiment would be within the scope of claim 24.

Regarding new claim 26 see paragraphs [0144] and [0249], which describe using oligonucleotides as PCR primers.

Supplemental Amendment/Response for application 10/037, 718 Applicants MCGINNIS ET AL. 19 November 20, 2005; 26 total pages submitted by fax to 571-273-8300

Regarding new claim 27 see [0181] and [0223] for support for the limitation *"y is 0.15"*.

Regarding new claim 28 The limitation "thousands of covering markers" is definite and supported as respectfully stated above under claims 14 and 24. The limitation "not human being" is discussed under claim 11.

Regarding new claim 29 some support for limitations in this claim are in [[0057] and [0058].

Regarding new claim 30 the limitation *"not human being"* has been discussed above under claim 11. Regarding the limitation *"the density of covering markers is at least thousands per chromosome"*, as stated above under claims 14 and 24, at the time of filing the whole field of association studies is anticipating using large numbers of markers (e.g., thousands) from high-resolution marker maps. These "thousands of bi-allelic markers" described in the application (e.g., [0249], [0324]) were anticipated at the time of filing to eventually be available for use in association linkage studies; and they were also anticipated to be potential trait-causing polymorphisms.

Examples of this expectation in the field given above under claims 14 and 24 are the Chee paper, the Risch paper and the Kruglyak paper. The Chee paper ([0341], endnote 8) is part of this application through incorporation by reference. The Chee paper describes a high-density array *"that could query the entire coding content of the human genome, estimated at 100, 000 genes"* (see p. 613, last sentence of the paper). A total of 100, 000 genes necessarily means a density of markers significantly higher than 5, 000 markers per chromosome. The Chee paper also describes high-resolution marker maps (p. 613 left most column).

As discussed above under claims 14 and 24, the Risch paper [0027], [0029] describes an association study using 500, 000 bi-allelic markers to test all genes in the human genome (estimated at 100, 000 genes). This is a density of 20, 000 or more markers per chromosome. The Kruglyak paper [0026], entitled *The use of a genetic map of bi-allelic markers in linkage studies*, is quoted in the application (see mid [0026]) as predicting "many acceptable SNPs" and a density of at least 1,000 SNPs (bi-allelic markers) per cM. This is equivalent to about at least 150, 000 bi-allelic markers per chromosome (or at least 3 million bi-allelic markers in the genome, see right column pp. 21, 22 of Kruglyak).

The present application describes "thousands of bi-allelic markers" (top [324]) in connection with the physical implementation of association scanning (testing) of a chromosome or chromosomal region (second sentence [0325]). Since a chromosomal region can be no longer than a chromosome, the density of such an association scan (or study) is at least thousands of covering markers per chromosome. The limitation *"wherein the density of covering markers is at least thousands of covering markers per chromosome"* is thus described and supported.

In addition, as respectfully submitted above under claim 14 and 24, the limitation *"thousands of bi-allelic covering markers"* is definite. In a similar manner, the limitation "*wherein the density of covering markers is at least thousands of covering markers per chromosome"* is also definite and is the degree of precision present in the art at the time of filing. "Thousands" is the plural of "thousand" meaning literally 2000 or more. Thousands is also a very large number. (See copy of page 1228 of the Tenth Edition of Merriam-Webster's Collegiate Dictionary giving the definition of "thousands" as plural of "thousand".)

In addition, the present application also describes the general increased power advantages of denser coverings (or studies) in [0182]. And denser studies of [0182] are contrasted with less dense studies (or coverings) of [0183]. Some examples of denser association coverings or studies are association studies (or coverings or scans) "*wherein the density of covering markers is at least thousands of covering markers per chromosome*".

Regarding new claim 31 the limitations in this claim regarding species have been discussed above under new claim 29.

Regarding new claim 32 For the limitation *wherein the CL-F region is a segment-subrange*; see [0185] *"Specific types of CL-F regions that are N covered are useful. For example, a rectangular CL-F region, a segment-subrange,..."*. For support for the limitation *wherein the segment of the segment-subrange is the subregion of interest or the chromosome* see claim 19 from which this claim depends. Specifically, claims 19 states "*wherein a chromosome or chromosomal subregion of interest is completely covered [by chromosomal segments]*". See also [0275] bottom of page 20 which states that the length of a chromosomal segment can be as long as a chromosome.
The clause *whereby the CL-F region is a rectangular region defined by the chromosome or subregion of interest in the chromosomal location dimension and defined by the subrange in the allele frequency dimension* is not a true limitation but follows directly from earlier limitations in the claim and the definition of a segment-subrange. See for example Definitions section [0090], [0092] and [0093].
For support for the limitation *"wherein each point in the CL-F region is N-covered to within [L, y] by markers belonging to a single subset, L is the length of the longest segment of the segments that cover the chromosome or subregion of interest, y is 0.15 and* $N \geq 2$," see claim19, from which this claim depends. Specifically, as stated in claim19, (1) the markers in each subset belong to only one segment whose maximum length is L, (2) the difference between the least common allele frequencies of any two subset markers does not exceed 0.15, and (3) there are two or more markers in each subset.

A similar concept is taught in the application: see [0099] and top [0100], *"A CL-F matrix is a collection of segment-subranges,....Each segment-subrange in the collection (or the matrix) is a CL-F matrix cell "* and see top [0186] *"In the case in which there are N or more markers within each cell of a CL-F matrix, then each point within the matrix is N covered to within the CL-F distance [$L_{.CM}$, W_{CM}], wherein $L_{.CM}$ is the length of a matrix cell and W_{CM} is the width of a matrix cell."* (In a CL-F matrix, each segment-subrange is the same length and width, i.e. each segment has the same length and each subrange is the same width.)

Some support for limitations in claim 19, are in the Set/Subset part of the application, [0301] to [0325]. A pictorial, nonlimiting example illustration and explanation of a Set/Subset N-covering was given on pages 18 and 19 of the Supplemental Amendment of Jan. 26, 2005 (the "Stamp Pasting Analogy" and "Illustration of an Example Set/Subset N-covering" **This nonlimiting example illustration and explanation is helpful, but not necessary, for understanding the invention defined by new claim 32.** The "Stamp Pasting Analogy" is reproduced below. And the "Illustration of an Example Set/Subset N-covering" will be faxed with copies of some published paper pages referred to herein. However, the Examiner may want to refer to the pictorial Illustration on page 19 of the Supplemental Amendment of January 26, 2005, as the quality of the mailed picture may be better than that of a faxed picture.

Stamp pasting analogy The N-covering that is taught in the Set/Subset Examples(s) is analogous to a teaching to paste different sized postage stamps (of maximum length L and width 0.15, each stamp containing a subset of two or more covering markers) over a large rectangle on a piece of paper so that all the points in the large rectangle are "covered" (stamp edges are, of course, parallel to the rectangle boundaries, it is possible for the stamps to overlap). Since each point in the large rectangle is "covered" (each point is underneath one or more stamps), then each point in the large rectangle is within the two-dimensional (CL-F) distance [L, 0.15] of two or more covering markers (N ≥ 2). This is explained in more detail with a pictorial illustration in the Illustration of an example Set/Subset N-covering using a CL-F map.

Regarding new claim 33 this claim has the limitation *"wherein the subrange of the CL-F region is the subrange 0 to less than 0.1"*. For support for this limitation see mid [0311] which describes covering the subrange *"below 0.1/above 0.9"*. That is, the least common allele frequency subrange 0 to less than 0.1; a bi-allelic polymorphism whose least common allele frequency is below 0.1 has a most common allele frequency above 0.9, the two frequencies sum to 1. And see also, e.g. bottom [0075] which says, *"the least common allele frequency coordinates of CL-F points in a particular CL-F region can range over only a very small subrange"* and gives an example of a subrange (the subrange 0.1 to 0.2) of small width (0.1). This width, 0.1, is the same as the width of the subrange 0 to less than 0.1.

Regarding new claim 34 contains the limitation *"N > 2"*. The limitation *"N ≥ 2"* in claim 32 (from which new claim 34 depends) literally means that N is greater than or equal to 2. As stated in [0182] *"In general, the greater N is, the greater the power of a version of the invention for linkage studies.* Because the greater N is, the greater the chance that linkage is detected..". Thus the specification supports higher values of N, i.e. N>2. See also top [0315] *"Hence, it is important that each subset contain multiple bi-allelic markers so that there is increased likelihood that at least one of the markers will be in reasonably strong disequilibrium with a closely linked bi-allelic disease locus."* Increasing the number of covering markers in each subset, as [0315] suggests, has the effect of increasing N.

Regarding new claims 35 and 36 the limitations in these claims have been discussed above under claims 32 and 33.

Regarding new claim 37 Newly added claim 37 contains the language "nearly identical" which caused the Examiner to reject canceled claim 10 for lack of definiteness. Newly added claim 37 deals with redundancy of markers and makes use of description recited in [0315], [0316] and [0317]. Similar description is found in [0268] to [0271]. See also [0321], which states that Step 3, the elimination of pairs of redundant markers in the same subset (that provide the same information), is not essential. That elimination of redundant markers in subsets, though not essential, is done in new claim 37.

Applicants respectfully submit that new claim 37 is definite. Specifically when markers are redundant and are in extreme positive linkage disequilibrium then every chromosome in the population that carries allele A also caries allele B and every chromosome that carries not allele A also carries not allele B, or this is nearly the situation [0316]. Under these circumstances the genotype of an individual at one marker will almost always predict the genotype of the individual at the other marker. Similarly allele frequency for an allele at one marker for a sample will predict with a very high degree of certainty or precision the allele frequency for an allele at the other marker.

Though there is relative language in claim 37. This relative language does not render the claim indefinite. As stated in the MPEP 2173.05(b) *"The fact that claim language, including terms of degree, may not be precise, does not automatically render the claim indefinite under 35 USC 112, second paragraph. (Seattle Box Co. v. Industrial Crating & Packing, Inc. 221 USPQ 568). Acceptability of the claim language depends on whether one of ordinary skill in the art would understand what is claimed in light of the specification."*

Supplemental Amendment/Response for application 10/037, 718 Applicants MCGINNIS ET AL. 23 November 20, 2005; 26 total pages submitted by fax to 571-273-8300

Applicants respectfully submit that the language used in claim 37 is as precise or accurate as the subject matter allows. It is not possible to reasonably specify parameters such as allele frequency differences or departures from maximal linkage disequilibrium between redundant markers with a greater degree of accuracy or precision. A clear result or effect of redundancy of markers (and the relative difference of "nearly identical information") is specified in the claim, specifically that there would be no increase in the likelihood of detecting linkage. The limitation is as follows: *"wherein the inclusion of a bi-allelic marker in the subset so that there would be a redundant pair in the subset would not increase the likelihood of detecting linkage and association of the trait-causing polymorphism".* Applicants respectfully submit the situation is similar to that in Orthokinetics, Inc. v. Safety Chairs, Inc. (1 USPQ 2d 1081), which is cited in MPEP 2173.05(b). In that case, the Court found that a claim to a chair "so dimensioned" as to fit between an automobile doorframe and one of the seats was definite. The Court said the phrase "so dimensioned" is as accurate or precise as the subject matter permits.

Similarly applicants respectfully submit that a redundant marker pair is defined in terms of what it does. The markers of the pair provide nearly identical information, and so the addition of one of the markers does not increase the likelihood of detecting linkage. This is similar to a functional limitation as described in MPEP 2173.05(g), which were found definite in In re Barr (170 USPQ 33) and In re Venezia (189 USPQ 149).

Regarding new claim 38 the limitations in this claim have been discussed above under claim 34.

Regarding new claim 39 this claim is essentially the same (and has the same scope) as previously filed (9/3/2003) former independent claim 3 which was allowed in the Notice of Allowance of 12/04/03, but was canceled to avoid a double patenting rejection in the parent, now abandoned. As with allowed independent claims 6 and 16, this claim has a slight change in terminology (compared to former claim 3) to make the claim more closely conform to the terminology in the Specification (see [0046], [0050]) and the new Abstract above.

Regarding new dependent claims 40, 41, 42 and 43 each of these claims depends from claim 39. The narrowing limitations in claim 40 are essentially the same as the narrowing limitations in previously allowed claims 7 and 17. And the narrowing limitations in claim 41 (*"thousands of covering markers"*), claim 42 (*"not human being"*) and claim 43 (species and covering marker number and density limitations) have been discussed above under claims 11, 14 and 24, 29 and 30.

Regarding new independent claim 44 This is an apparatus claim. Similar, previously filed apparatus claims in a parent application (09/623, 068) in means plus function format were rejected on two points in an Office Action dated 10/19/2004. The first point (bottom p. 2 and top p. 3) was stated as *"there is no clear indication in the specification as to what actual elements or components are contemplated in the claimed apparatus, let alone why such an apparatus might be patentable"*. The second point was an indefiniteness rejection under 35 USC 112, 2nd paragraph. And the Examiner suggested *"if applicants are interested in apparatus-type claims in future applications, they may wish to consider non-means plus function claims which clearly specify the apparatus components"*.

Applicants respectfully submit that this new claim 44 addresses each point of rejection. Specific apparatus and element limitations (high-density array of oligonucleotides, a nylon membrane with sequence-specific oligonucleotides bound to the membrane, or is oligonucleotides bound to a glass slide or a silicon chip) are recited in the claim. Some particular support for these in the specification is found in [0208] which refers to d) in Process#1. Paragraph [0163] describes "Oligonucleotide Technology" as a way to practice d). And paragraphs [0249] with references (1) and (2) in endnote 11, and [0247], [0144] describe Oligonucleotide Technology with the specific apparatus and element limitations recited in the claim. References (1) and (2) are incorporated by reference into the application, and a copy of page 6230 of reference (2) will be faxed under separate cover.

As to the question of patentability of the apparatus, applicants respectfully submit the following explanation. Claim 44 contains the limitation *"wherein one or more copies of a set of oligonucleotides that is complementary to the group of two or more bi-allelic covering markers is used by the apparatus to determine the data, wherein the oligonucleotides in each complementary set are attached to the apparatus "*. Some support for this limitation in connection with Oligonucleotide Technology is in [0259], [0260], [0144], [0249], [0325] and p. 6230 of reference (2) (paragraph above) that describes oligonucleotides bound to a nylon membrane. One or more copies of such a set of complementary oligonucleotides are novel and unobvious. **Indeed claims 16-19 in this application are directed to such one or more copies of a set of oligonucleotides and have been previously allowed by the Examiner as patentable.**

Such a novel and unobvious set of oligonucleotides makes the structure of the apparatus novel and unobvious as well. The oligonucleotides in the complementary set (or copies of the set) are bound or mounted (or immobilized) in some way to structures in the apparatus. Thus the structure of the apparatus distinguishes it from prior art, essentially fulfilling the criterion of MPEP 21114 (APPARATUS CLAIMS MUST BE STRUCTURALLY DISTINGUISHABLE FROM PRIOR ART).

Applicants respectfully submit that a similar situation is when a general purpose computer is programmed to become a special purpose computer. When a general purpose computer is programmed to carry out an algorithm, *"such programming creates a new machine, because a general purpose computer in effect becomes a special purpose computer once it is programmed to perform particular functions pursuant to instructions from program software"*. The quote is from In re Alappat (31 USPQ2d 1545, 1548; 33 F.3d 1526, 1545).

Regarding new claim 45 this claim depends from claim 44 and the narrowing limitations in this claim are essentially the same as the narrowing limitations in previously allowed claims 7 and 17.

Regarding new claims 46-49 the narrowing limitations in these claims (*"thousands of covering markers"*, *"not human being"* and *"high-density array of oligonucleotides"*), have been discussed above under claims 11, 14 and 24, and 44.

Regarding new claims 50 and 51 the narrowing limitations in these claims *"not human being"*, *"density of covering markers is at least thousands per chromosome"*, and *"the species is a paleospecies, a species hybrid.....or a plant species"* have been discussed above under claims 11, 29 and 30.

Regarding the new Abstract The content of the new Abstract is similar to the content of previous Abstracts in the present application and in parent application PCT/US/04376. The new Abstract sketches versions of the invention in the presently allowed and pending claims. Some support for the new Abstract is in the Brief Description Section ([0046], [0047], [0048], [0050], [0052]), and Definitions ([0079], [0059], [0007]) and theory [0031], [0271], [0283], [0285].

Supplemental Amendment/Response for application 10/037, 718 Applicants MCGINNIS ET AL. 26
November 20, 2005; 26 total pages submitted by fax to 571-273-8300

Conclusion

An RCE has been filed in the previous Amendment/Response of September 13, 2005 and fees have been paid. The previous Amendment/Response of September 13, 2005 addressed each point of rejection in the Final Office Action of 5/13/2005.

Claims 6-9 and 15-19 were allowed in the Final Office Action mailed May 13, 2005. Claims 10-14 and 20-24 were rejected in that Final Office Action. In the present Supplemental Amendment/Response, in response to the rejections in the Final Office Action applicants have canceled claims 10, 12, 13, 20, 22 and 23; and claims 14, 21 and 24 have been amended. Clarification regarding claims 14 and 24 was also respectfully submitted.

Remarks/Arguments in this Supplemental Amendment/Response have also addressed each point of rejection in the Final Office Action. Applicants have also amended allowed claims 6 and 16 with a slight change in terminology to make the claims more closely conform to the terminology in the Specification and newly amended Abstract above. These amendments did not, however, change the scope of either claim. New claims 26-47 have been added and extra claim fees have been paid. New claim 39 is, however, essentially the same (same scope) as former independent claim 3, filed 9/03/2003, which was subsequently allowed, but was canceled to avoid a double patenting rejection in the parent application 09/947, 768, now abandoned. have been amended in response to the Examiner's rejection in the Final Office Action of 5/13/2005. The Abstract has also been amended.

For the reasons advanced above, applicants respectfully submit that the application is now in condition for allowance and that action is earnestly solicited.

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